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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,568	04/07/2005	Eric Adriaenssens	123439	8995

25944 7590 02/22/2008

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EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
02/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,568	ADRIAENSSENS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Claims 23-31 are pending and are under examination.

- 35 USC § 112 2nd paragraph rejection withdrawn

The rejection of claims 30 for being indefinite is withdrawn in view of the cancellation of Applicants amendment to claim 30.

35 USC § 102(b) rejections withdrawn

The rejection of claims 23 and 31 under 35 USC 103(a) as being as being anticipated by Sakamoto et al is withdrawn in view of Applicants amendment to claim 23.

35 USC § 103(a) rejections maintained

The rejection of claims 24- 27, 29 and amended claim 30 under 35 U.S.C. 103(a) as being unpatentable over Sakmoto et al, in view of WO 97/38313 and Varilek et al is maintained.

Applicants argue that Sakamoto et al fails to teach all the features of independent claim 23 and that WO 97/38313 and Varilek et al fail to cure the deficiencies. However, WO 97/38313 teaches how to enrich cancer cells from various

bodily fluids (page 3, lines 1-17, page 6, line 3 to page 18 line 28). Thus WO 97/38313 does teach the added limitation of claim 23 and does cure the deficiency of Sakamoto.

The rejection of claims 28 under 35 U.S.C. 103(a) as being unpatentable over Sakmoto et al, in view of WO 97/38313 and Picker et al is maintained.

Applicants argue that Sakamoto et al fails to teach all the features of independent claim 23 and that WO 97/38313 and Picker et al fail to cure the deficiencies. However, WO 97/38313 teaches how to enrich cancer cells from various bodily fluids (page 3, lines 1-17, page 6, line 3 to page 18 line 28). Thus WO 97/38313 does teach the added limitation of claim 23 and does cure the deficiency of Sakamoto.

NEW REJECTIONS:

Claim Objections

Dependent claim 31 is objected to as being broader than claim 23, the claim that claim 31 depends from. Claim 31 is drawn to a method for the early diagnosis, screening, therapeutic follow-up, prognosis and the diagnosis of relapse in the case of breast cancer. Claim 23 is drawn to a method for the diagnosis of breast cancer comprising determining the presence of NGF in a biological sample obtained from a patient suspected of suffering from breast cancer.

Claim Rejections - 35 USC § 112

Claims 23 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the diagnosis of breast cancer, does not reasonably provide enablement for a method of therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method for the early diagnosis, screening, therapeutic follow-up, prognosis and the diagnosis of relapse in the case of breast cancer comprising determining the presence of NGF in a biological sample obtained from a patient suspected of suffering from breast cancer, wherein the biological sample is selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid, urine and effusions.

The specification discloses that NGF was detected in biopsies of human breast cancer. (Example 5). There is no disclosure in the specification on the detection of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine or effusions.

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and associated markers such as CIN and HLA alleles and HPV type. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be

validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4). It is clear that the art teaches the necessary experimentation and data required to allow one of skill in the art to predict the method of therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer using the biomarker NGF, and the specification has not provided guidance or examples to predict the therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer by determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine and effusions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakmoto et al, further in view of WO 97/38313 and Varilek et al (cited previously).

The claims are drawn to a method for the diagnosis of breast cancer consisting of determining the presence of NGF in a biological fluid derived from a patient suspected of suffering from breast cancer, wherein the biological sample consist of biological fluid comprising circulating tumor cells, wherein circulating tumor cells secreting NGF are isolated and cultured under conditions such that they secrete NGF.

Sakamoto et al has been described supra.

Sakamoto et al does not teach enriching cancer cells from bodily fluids, culturing the cells such that they secrete NGF nor demonstrating NGF using NGF-sensitive cells.

WO 97/38313 teaches how to enrich cancer cells from various bodily fluids (page 3, lines 1-17, page 6, line 3 to page 18 line 28).

Varilek et al describe the secretion of NGF from an adenoma cell line. (page G447 1st column 1st paragraph) Varilek et al further describes the detection of secreted NGF by culturing a biological sample in the presence of the NGF-sensitive cell, PC-12. (page G446, 2nd paragraph).

One of ordinary skill in the art would have been motivated to apply WO 97/38313 method of enriching cancer cells from bodily fluids to Sakamoto et al's method for diagnosing breast cancer by detecting NGF because enriching for and detecting cancer cells in the peripheral blood would be of great diagnostic benefit. (WO 97/38313, page 1 lines 14-17). One of ordinary skill in the art would have been motivated to apply Varilek et al method of detecting NGF from cell supernatants to WO 97/38313 and Sakamoto et al's method of enriching breast cancer cells from bodily fluids because of the sensitivity of detecting NGF from cell supernatants. (Varilek et al, Abstract)

Thus it would have been prima facie obvious to one skilled in the art to have combined WO 97/38313 and Sakamoto et al's method of enriching breast cancer cells from bodily fluids with Varilek et al method of detecting NGF from cell supernatants to detect NGF in cell supernatants from isolated breast cancer cells for diagnosing breast cancer.

Claims 23 and 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Sakamoto et al (cited previously) in view of Bigazzi et al (Clin Endocrinol, 1977, 6:105-112) and Pica et al (AIDS, 1998, 12:2025-2029).

The claims are drawn to a method for the diagnosis of breast cancer comprising determining the presence of NGF in a biological sample obtained from a patient suspected of suffering from breast cancer, wherein the biological sample is selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid, urine and effusions.

Sakamoto et al disclose a method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF (page 975, 2nd column, 3rd paragraph).

Sakamoto et al does not disclose determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine or effusions. (Taber 1).

Bigazzi et al detected high levels of NGF in the serum of a patient with medullary carcinoma of the thyroid gland.

Pica et al detected high serum levels of patients with Kaposi's sarcoma. (Table 1).

One of ordinary skill in the art would have been motivated to apply Bigazzi et al and Pica et al's detection of NGF in the serum to Sakamoto et al's method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF because of the simplicity of detecting a tumor antigen in serum as opposed to a tissue biopsy. I would have been prima facie obvious to combine Sakamoto et al's method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF with Bigazzi et al and Pica et al's detection of NGF in the serum to simplify the assay for NGF in breast cancer.

Applicants argue that demonstrate that tissue expression does not necessarily correlate with plasma expression. Applicants cite Kuvaja et al, Shimonishi et al and

Koopmann et al to support their argument. It is noted that Applicants have not demonstrated that serum levels of NGF are indicative of colorectal cancer.

Applicant's arguments have been fully considered but they are not persuasive. Kuvaja et al discloses that there are different forms of circulating MMP-2 in breast cancer which may help the explain the conflicting reports as to the correlation of MMP-2 and breast cancer. (page 1320, 2nd paragraph). Kuvaja et al further states that one rep[ort found that high levels of MMP-2 in serum correlated with advanced stage and higher lymph node status as well as an adverse prognosis in breast cancer patients. (page 1321, 1st column). Shimonishi et al discloses that galectin-1 and gelectin-3 have been shown to be tumor markers for some malignant tumors but their importance as tumor markers appears to be cancer type dependent. (page 301, 2nd paragraph and page page 309, 1st paragraph). It is noted that the paragraph cited by Applicants demonstrated that galectin-3 overexpressoin was related to the type of intrahepatic cholangiocarcinoma and did not indicate that tissue expression of galectin-3 was not correlated with expression of galectin-3 in the serum. Koopman et al does disclose that levels of Mac-2BP, the receptor for galectin-3, were not elevated in serum, but suggested that the reason for this may be due to the up-regulation of Mac-2BP in response to a variety of nonmalignant inflammatory conditions. (page 1614, 1st column). Thus, the references cited by Applicants do not support their argument that tissue expression does not necessarily correlate with plasma expression except when levels of the purported tumor antigen are elevated in serum in response to another stimuli.

Summary

Claims 23-31 stand rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax

phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson
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571-272-6539

/MISOOK YU/

Primary Examiner, Art Unit 1642